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(54) TREATMENT OF SCHIZOPHRENIA BY CHOLINESTERASE INHIBITORS

BEHANDLUNG VON SCHIZOPHRENIE MIT HILFE VON CHOLINESTERASEINHIBITOREN

TRAITEMENT DE LA SCHIZOPHRENIE A L'AIDE D'INHIBITEURS DE CHOLINESTERASE

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Description

[0001] The present invention relates to the use of cholinesterase inhibitors, such a galanthamine, for the preparation of a pharmaceutical composition for the treatment of schizophrenia, in particular affective or schizoaffective type of schizophrenia.

GENERAL BACKGROUND

[0002] Benzodiazepines eg. diazepam, dipotassiumchlorazepate, chlorazepate, chlordiazepid, medazepam, flurazepam, clobazam, clonazepam, nitrazepam, flunitrazepam, estazolam, bromazepam, alprazolam, lorasepam, lormetazepam, oxazepam, temazepam, brotizolam, triazolam, chlordiazepam, halazepam or prazepam have been used for several decades, but have become increasingly popular because of their effects and their low toxicity compared to other drugs of similar actions.

[0003] The major known effects of benzodiazepines are

- anticonvulsant
- muscle relaxing
- sedative
- hypnotic
- anxiolytic
- antipsychotic.

[0004] Thus, the benzodiazepines are relevant as drugs in connection with a broad spectrum of diseases, including schizophrenia.

[0005] The mechanism of effect of the benzodiazepine drugs are unknown, but is believed to be an effect on the GABA-system of the central nervous system. However, the effect of the benzodiazepines seems to be some kind of an overall unspecific inhibition of the central nervous system independent of the transmitter in the regions affected.

[0006] When using benzodiazepines, some of their effects are desirable, but other may be considered as side effects with respect to the specific disease treated.

[0007] When any of the anticonvulsant, the muscle relaxing, the anxiolytic or the antipsychotic effects are desired, it is often a problem that the sedative and hypnotic effects of benzodiazepines prohibit the use of high dosages of benzodiazepines, or, when such high dosages are nevertheless necessary to get a reasonable effect of the treatment, make it necessary to hospitalize the patient. Even in the dosages used, e.g. against anxiety, the sedative effect of benzodiazepines may be disadvantageous.

DETAILED DISCLOSURE OF THE INVENTION

[0008] It has surprisingly been found that a cholinesterase inhibitor counteracts the typical sedative and the hypnotic effects of benzodiazepines in a broad spectrum of diseases including schizophrenia and affective type schizophrenia. Furthermore it has been found that a cholinesterase inhibitor can be used alone to combat schizophrenia and affective type schizophrenia and thereby overcome the disadvantageous sedative and hypnotic effects of benzodiazepine therapy.

[0009] The dosage of the cholinesterase inhibitor, such as galanthamine, which will be effective in each particular case, can suitably be found by monitoring each patient individually, or may be assessed on the basis of experience gained. A more detailed discussion of suitable dosage ranges is given in the following.

[0010] Schizophrenia and affective type schizophrenia, and schizo-affective type of schizophrenia are conditions which according to the present invention may be treated with a cholinesterase inhibitor alone, or with a cholinesterase inhibitor as the main functional drug with respect to the treatment of the schizophrenia in question.

[0011] In the treatment of the above-mentioned types of schizophrenia, the cholinesterase inhibitor may, according to the present invention, be used as the sole or main drug in the treatment of not only the apathoabulic manifestation of the schizophrenia but also for other manifestations, especially for the affective type schizophrenia. This is important to note in view of the fact that Vovin et al. (Correction of apathetic-abulic manifestations of schizophrenia with cholinotropic drugs, Zhurnal Nevropatol Psikhiatr. 1991(2), 111-115) disclose the use of galanthamine or desoxypeganin together with benactizin for the treatment of the apatho-abulic manifestations of schizophrenia; the paper contains no indication of the use of galanthamine or any other cholinesterase alone or as the main drug.

[0012] Compounds which function as cholinesterase inhibitors may be divided into several groups, namely poison gases for use in warfare, insecticides, such as malathion, and drugs. In the present context, the term "pharmaceutically acceptable" indicates that the cholinesterase inhibitors in question are not such which will be poisonous, in other words,

they pertain to the drug group and not to the poison group.

[0013] Pharmaceutically acceptable cholinesterase inhibitors are, e.g., physostigmine, tacrine and tacrine analogues, galanthamine, epigalanthamine, norgalanthamine, fasciculin, metrifonate, heptyl-physostigmine, norpyridostigmine, norneostigmine, and huperzine. Some of the cholinesterase inhibitors show certain undesirable properties, such as short half life, etc. In some cases, such deficiencies can be compensated for by modifying the compound into a prodrug for the active compound, in accordance with well-known principles for prodrug construction, such as introduction of hydrophilic groups to enhance the solubility of a compound in water, thus making it possible to formulate the compound as a an injection solution, an introduction of lipophilic groups such as ester groups to enhance the capability of the compound to pass the blood-brain barrier.

[0014] The presently preferred cholinesterase inhibitor used according to the invention is galanthamine. Galanthamine is known as an acetylcholinesterase acting substantially only at nicotinic receptor sites, that is, having a high selectivity for acetylcholinesterase as opposed to butyrylcholinesterase. A more detailed discussion of galanthamine and galanthamine derivatives is given below:

[0015] Galanthamine is a well-known acetylcholinesterase inhibitor which is active substantially selectively at nicotinic receptor sites and has substantially no effect on muscarinic receptor sides, is capable of passing the blood-brain barrier in humans, and presents no severe side effects in therapeutically necessary dosages.

[0016] Galanthamine and acid addition salts thereof have, for many years, been known to have anticholinesterase properties.

[0017] Galanthamine, a tertiary alkaloid, has been isolated form the bulbs of the Caucasian snowdrops Galantanus woronowi (Proskurnina, N.F. and Yakoleva, A.P. 1952, Alkaloids of Galanthus woronowi. II. Isolation of a new alkaloid. (In Russian.) Zh. Obschchei Khim. (J.Gen.Chem.) 22, 1899-1902. Chem.abs. 47,6959, 1953. It has also been isolated from the common snowdrop Galanthus Nivalis (Boit, 1954).

[0018] Galanthamine has been used extensively as a curare reversal agent in anaesthetic practice in Eastern bloc countries (cf. review by Paskow, 1986) and also experimentally in the West (cf. Bretagne and Valetta, 1965: Wislicki, 1967; Conzanitis, 1971).

[0019] Pharmacokinetic studies have recently been made by Thomsen, T. and H. Kewitz. (Selective Inhibition of Human Acetylcholinesterase by Galanthamine in vitro and in vivo. Life Sciences, Vol 46, pp. 1553-1558 (1990), and, by the same authors, Galanthamine Hydrobromide in a Long-Term Treatment of Alzheimer's Disease. Dementia 1990, 1:46-51).

[0020] It is believed that the excellent and surprising effect possessed by galanthamine is due to its specific-profile of properties, the most important of the known ones of which can be summarized as follows:

- capability to pass the blood brain barrier in humans,
- a high selectivity for acetylcholinesterase as opposed to butyrylcholinesterase (about 50-fold when measured by the in vitro method by Thomsen et al., see below),
- a sufficient elimination half life to warrant duration of an effective concentration of at least 4 hours, probably at least 6 hours,
- a relatively low toxicity in therapeutical concentrations,
- capability of being effective in doses which are sufficiently low to keep peripheral side effects low.

[0021] Galanthamine must be considered as being a very desirable drug for the treatment according to the invention: The elimination half life of galanthamine hydrobromide is over four hours; it shows a practically complete renal elimination. A complete elimination of metabolites and galanthamine takes place in 72 hours. Galanthamine has been used in Eastern Block countries since around 1958 as an anticurare agent in anesthesiology, and a considerably number of patients have been treated with galanthamine without any reported case of liver toxicity or serious side effects. Galanthamine hydrobromide, being a tertiary amine and lipid soluble, is absorbed rapidly from the gut and transverses the blood brain barrier easily. The common side effects, other than the ones related to cholinergic crisis, are either nausea or vomiting, and a slight headache. However, these side effects are rare, especially when care is taken to start medication in low doses such as mentioned above.

[0022] The galanthamine can suitably be administered orally in the form of an acid addition salt, e.g. the hydrobromide, but other administration forms are possible and realistic, such as is described below.

[0023] Because galanthamine has substantially no effect on the activity at muscarinic receptor sites, as apparent from its high selectivity for acetylcholinesterase as opposed to butyrylcholinesterase, it will not give rise to the often severe side effects on the heart which are associated with cholinesterase inhibitors which have a low selectivity for acetylcho-

linesterase as opposed to butyrylcholinesterase. Galanthamine has an in vitro selectivity for acetylcholinesterase opposed the effect on butyrylcholinesterase of 50 to 1, as reported by Thomsen, Life Sciences, Vol 46, pp. 1553-1558 (1990).

[0024] As indicated above, the amount of galanthamine is preferably adjusted individually based upon observation of the effect of initially very low dosages. There is as considerable difference with respect to how sensitive individuals are to acetylcholinesterase inhibitors. Thus, the amount of galanthamine is suitably adjusted by means of a regimen starting at low dosages, e.g. 1 mg, preferably at 5 mg, per day, but, if appropriate, even as low as 0.1 mg per day, if the dosage is well tolerated by the patient within the first two hours the dosages is increased to, e.g. 10 mg per dosage dosed 3 to 4 times per day or in some severe cases to 60 mg or more per day dosed over 3 or 4 times.

[0025] Because cholinergic crisis, a life-threatening dose-dependant side effect of all kinds of acetylcholinesterase inhibitors, should, by all means, be avoided, it is recommended to start with the low dosages as mentioned above and furthermore not to exceed 150 mg per day and preferably not to exceed dosages above 60 mg per day, unless the patient shows a very low sensitivity to acetylcholinesterase inhibitor, in which case higher doses, such as 200 mg per day, could be used.

[0026] While galanthamine has, indeed, given remarkable results, such as appears from the clinical cases given in the examples, it is justified to presume that other acetylcholinesterase inhibitors which are functional equivalents to galanthamine with respect to its combination of high selectivity with respect to nicotinic receptor sites and capability of passing the blood brain barrier in humans in vivo, will also show a useful combination of effect against the sedative or hypnotic effects of benzodiazepines and acceptability in the clinic, although it cannot be ruled out that galanthamine, galanthamine salts and galanthamine derivatives, due to the special conformation of the galanthamine ring system, have specific properties which are decisive for the remarkable effect.

[0027] In accordance with the above, compounds which are functional equivalents of galanthamine are defined herein as compounds which

a) possess an at least 10-fold selectivity, preferably an at least 20-fold selectivity, more preferably an at least 40-fold selectivity, and most preferably an at least 50 fold selectivity, for acetylcholinesterase as opposed to butyrylcholinesterase, when measured by the in vitro method by Thomsen et al., see below,

b) are capable of passing the blood brain barrier in humans in vivo.

[0028] As will be understood from the above definition, a compound can be subjected to well-defined and relatively short-lasting tests (see below) to determine whether it fulfills criterion a) above. Then, the likelihood whether the compound will pass the blood brain barrier in humans in vivo (criterion b)) can be assessed in a model. One such model is a whole rat brain model in which rats are given the acetylcholine esterase in vivo and are then killed whereupon homogenate of the rat brain is examined with respect to the acetylcholinesterase activity; the result is then compared to the acetylcholinesterase activity in rat brains not treated with acetylcholinesterase inhibitors. Another rat model could be the measurement and comparison of acetylcholinesterase activity in cerebrospinal fluid in vivo in the same rat before and after treatment. If the compound fulfills criterion a), and its likelihood of passing the blood brain barrier has been established in one of the above-described rat brain models, it will be a candidate drug. An initial determination of toxicity is necessary in cases before any effect in humans can be assessed; such initial determination of toxicity can be performed by pharmacologic tests in a manner known per se. After the pharmacological tests, the capability of the candidate drug of passing the blood brain barrier in humans in vivo can be determined by the method described below. If the candidate drug has been found to possess this capability, it can be passed to the testing proper. Optionally, the candidate drug can be subjected to additional short-lasting tests, such as the in vivo selectivity test described by Thomsen et al., and a test to determine whether it increases cortisol level in humans. Both of these tests give further indication of whether the candidate drug has a spectrum of properties equivalent to galanthamine with respect to what must be presumed to be essential properties. Peripheral side effects will be assessable when the effect is tested clinically, which is acceptable from an experimental and ethical point of view, provided the toxicity has first been assessed by the above-mentioned pharmacological tests. With respect to the final assessment of the candidate drug's effect on the sedative or hypnotic effects of benzodiazepines, a rational and efficient design of the assessment will involve an initial test on one or a few patients and, provided the initial test is positive, the above-mentioned conclusive double blind test. Because of the well-defined and brief character of all of the tests, and especially the well-defined in vitro character of the initial screening, the test series for identifying useful functional equivalents of galanthamine is a reasonable an not burdensome routine which is within the realm of the person skilled in the art.

[0029] Functional equivalents and derivatives of galanthamine which are useful in the method of the invention will be employed in the same manner as stated herein for galanthamine. Whenever quantities of such a functional equivalent or derivative are referred to herein, the quantities are given as the equipotent quantity of galanthamine hydrobromide with respect to inhibition of acetylcholinesterase, that is, as the quantity of galanthamine hydrobromide which results in

the same inhibition of acetylcholine esterase in the above-mentioned in vitro test according to Thomsen et al as does the functional derivative or derivative.

[0030] The selectivity of the acetylcholinesterase inhibitor for acetylcholinesterase as opposed to butyrylcholinesterase can be determined by in vitro and in vivo tests as described by Thomsen and Kewitz in the above mentioned paper Selective Inhibition of Human Acetylcholinesterase by Galanthamine in vitro and in vivo, Life Sciences, Vol 46, pp. 1553-1558 (1990), and T. Thomsen, H. Kewitz and O. Pleul, J. Clin. Chem. Clin. Biochem. 26 469-475 (1988). The in vitro test described by Thomsen and Kewitz in Life Sciences, Vol 46, pp 1553-1558 (1990) is the one referred to above in connection with criterion a) and whenever numeric (10-fold, 20-fold, 40-fold) reference to selectivity for acetylcholinesterase as opposed to butyrylcholinesterase is made in the claims. According to Thomsen and Kewitz, galanthamine hydrobromide, when tested under the conditions described, shows a 50-fold selectivity; this selectivity value is taken as the "fixpoint" whenever in vitro selectivities are discussed herein and could be used, for the purpose of determining the selectivities for other cholinesterase inhibitors, as a calibration value which is the one to establish with galanthamine hydrobromide in any repetition of the experiment described by Thomsen and Kewitz. Thus, with reference to this determination method, a preferred acetylcholinesterase inhibitor is one which in the in vitro method described has an at least 10-fold selectivity for acetylcholinesterase as opposed to butyrylcholinesterase, such as an at least 20-fold selectivity for acetylcholinesterase as opposed to butyrylcholinesterase, e.g. an at least 40-fold selectivity for acetylcholinesterase as opposed to butyrylcholinesterase.

[0031] A relatively easy commercially available selectivity test which can be used as a practical tool in the screening of candidate drugs is the test described in Example 1 herein.

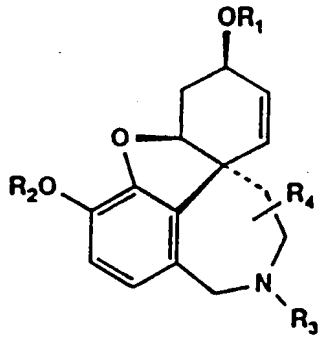
[0032] The capability to pass the blood brain barrier in vivo in humans can be assessed by either by a test which could be called "Auditory brain stem response" or by a test which is based on the measurement of CRH, ACTH and cortisol. The rationale behind these tests, and the way they are performed, is explained in the following:

[0033] The auditory brain stem response test is based on the observation that manio-depressive patients are hypersensitive to cholinergic influences, one manifestation hereof being hypersensitivity to auditory signals as assessed by the increase of amplitude of auditory evoked potentials in the nuclei of the auditory system in the brain stem, i.e. on the "brain side" of the blood brain barrier. This hypersensitivity manifests itself in a lower amplitude than in normal humans when the person is not treated with a cholinergic agent such as acetylcholinesterase inhibitor; and a very significantly increase of the amplitude when the person has received a cholinergic agent, provided, of course, that the cholinergic agent is able to pass the blood brain barrier and thus enter the nuclei of the auditory system in the brain stem. See also example 3.

[0034] The other test based on the measurement of CRH (corticotropic-hormone releasing hormone released from the hypothalamus in the brain, and which releases both ACTH from the adenohypophysis and cortisol from the adrenal medulla) and ACTH (corticotropic hormone, which releases cortisol from the adrenal medulla) is carried out by measuring the CRH, ACTH and cortisol concentration in the blood in healthy persons before and after medication with acetylcholinesterase. If the concentration of all three hormone are increased after medication or at least CRH and cortisol are increased it is proven that the acetylcholinesterase has effect in the central nervous system, and since it is an in vivo experiment it is further proven that the acetylcholinesterase has passed the blood brain barrier.

[0035] As mentioned above, the selectivity of the acetylcholinesterase inhibitor can, as an additional characterization, optionally be expressed with reference to the in vivo determinations performed by Thomsen and Kewitz on galanthamine and described in the above-mentioned paper Selective Inhibition of Human Acetylcholinesterase by Galanthamine in vitro and in vivo, Life Sciences, Vol 46, pp. 1553-1558 (1990). With reference to this determination, a preferred acetylcholinesterase inhibitor is one which, upon administration in an amount of 10 mg to a healthy adult, results in inhibition of at least 40% of the acetylcholinesterase activity in erythrocytes from the adult within about 2-5 minutes and no substantial inhibition of butyrylcholinesterase therein, such as an acetylcholinesterase inhibitor which, when administered in an amount of 10 mg to a healthy adult, results in inhibition of at least 50% of the acetylcholinesterase activity in erythrocytes from the adult within about 2-5 minutes. For galanthamine, Thomsen and Kewitz found 65% inhibition of acetylcholinesterase in the erythrocytes within 2 minutes after administration of 10 mg of galanthamine i.v. in a healthy volunteer, whereas no inhibition of butyrylcholinesterase in plasma was seen. Also these determinations are referred to in claims herein and should, in connection with the evaluation of the corresponding selectivities of candidate drugs different from galanthamine hydrobromide be considered the "calibration fixpoints" which will be established with galanthamine hydrobromide in any repetition of this experiment.

[0036] As mentioned above, it is possible that galanthamine, galanthamine salts and galanthamine derivatives, due to the special conformation of the galanthamine ring system, have specific properties which are decisive for the remarkable effect established according to the present invention. Thus, according to one aspect of the invention, compounds which are contemplated to be valuable and useful in the treatment according to the invention are the compounds having the formula I (formula I also represent galanthamine itself)



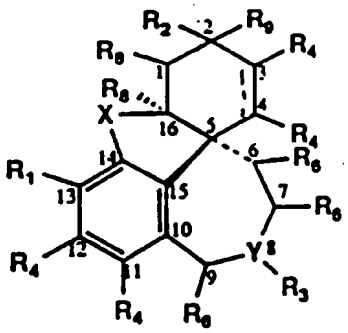
I

wherein R^1 and R^2 which may be the same or different each represents a hydrogen atom or an acyl group, such as a lower alkanoyl group, e.g. an acetyl group or a straight-chained or branched alkyl group, e.g. methyl, ethyl, propyl, or isopropyl; R^3 is a straight or branched chain alkyl, alkenyl or alkaryl group which is optionally substituted by a halogen atom or a cycloalkyl, hydroxy, alkoxy, nitro, amino, aminoalkyl, acylamino, heteroaryl, heteroaryl-alkyl, aroyl, aroylalkyl or cyano group; and R^4 represents a hydrogen or halogen atom attached to at least one of the ring carbons of the tetracyclic skeleton, with the proviso that when R^4 is in a position neighbouring the nitrogen atom, then R^4 is preferably different from halogen, and salts thereof, such as a hydrobromide, hydrochloride, methylsulphate or methiodide.

[0037] In the compounds of formula I, alkyl moieties preferably contain 1 to 8 carbon atoms, halogen atoms are preferably fluorine, chlorine, or bromine, especially fluorine or chlorine, aryl moieties are preferably phenyl, cycloalkyl groups are preferably 3- to 7-membered rings, especially cyclopropyl or cyclobutyl, and heteroaryl moieties are preferably 5- to 8-membered rings, e.g., thienyl, furyl, pyridyl, pyrrolyl, or pyrizanyl.

[0038] Among the compounds of the formula I are those described in EP-A-236684. The compounds of formula I may be prepared according to conventional techniques, including those described in EP-A-236684.

[0039] A broader range of compounds which, from the point of view of structural similarity with galanthamine, are contemplated to be valuable compounds useful in the method of the invention are galanthamine derivatives of the general formula II



II

wherein the broken line represents an optionally present double bond between carbon atoms 3 and 4, R_1 and R_2 are each selected independently from the group consisting of hydrogen, hydroxyl, amino or alkylamino, cyano, sulfhydryl, alkoxy of 1-6 carbon atoms, alkylthio, aryloxy, arylthio, R_5-substituted aryloxy, R_5-substituted arylthio, aralkoxy, an aliphatic or aryl carbamyl group wherein the aliphatic or aryl moiety may be R_5 substituted or unsubstituted, aralkylthio, R_5-substituted aralkoxy, R_5-substituted aralkylthio, aryloxymethyl, R_5-substituted aryloxymethyl, alkanoyloxy, hydroxy-substituted alkanoyloxy, benzoyloxy, R_5-substituted benzoyloxy, aryloxycarbonyl and R_5-substituted aryloxycarbonyl, R_1 may also be alkyl of up to 14 carbon atoms, or hydroxymethyl, R_2 may also be carboxymethyl, provided that at least one of R_1 and R_2 is hydroxy, amino or alkylamino unless R_8 is hydroxyme-

thyl,

R_3 is hydrogen, straight or branched chain alkyl of 1-6 carbon atoms, cycloalkylmethyl, phenyl, R_5-substituted phenyl, alkylphenyl, R_5-substituted alkylphenyl, heterocyclyl selected from α- or β-furyl, α- or β-thienyl, thenyl, pyridyl, pyrazinyl, and pyrimidyl, alkyl-heterocyclyl or R'-substituted heterocyclyl, where R' is alkyl or alkoxy,

each R_4 is independently selected from hydrogen, hydroxyl, sulfhydryl, alkyl, aryl, aralkyl, alkoxy, mercaptoalkyl, aryloxy, thiaryloxy, alkaryloxy, mercaptoalkaryl, nitro, amino, N-alkylamino, N-arylamino, N-alkarylamino, fluoro, chloro, bromo, iodo, and trifluoromethyl,

R_5 is selected from the same groups as R_4,

R_6 is hydrogen, halo, trifluoromethyl or alkyl of 1 to 4 carbon atoms, with the proviso that when R^6 is in position 7 or 9, it is preferably not halo.

R_8 is hydrogen or hydroxymethyl,

R_9 is hydrogen or alkyl of 1 to 6 carbon atoms, or when R_2 is hydroxyl, R_9 may be a moiety of formula II wherein R_9 is hydrogen and R_2 is a linking bond; or

R_2 and R_9 may jointly form semicarbazone,

X is oxygen or NR_5,

Y is nitrogen or phosphorus,

and methylenedioxy derivatives thereof with the proviso that when X is O, R_3 is not methyl when R_1 is methoxy, R_2 is hydroxy, and all R_4 are hydrogen,
or a pharmaceutically acceptable acid addition salt thereof.

[0040] Examples of subclasses and specific compounds of the formula II are given in WO 88/08708, which also discloses methods for preparing the compounds II.

[0041] Galanthamine, galanthamine salts, galanthamine derivatives and galanthamine functional equivalents, when suited there-for, may be administered orally at a dosage of e.g. 5-150 mg per day, such as 10-60 mg per day, e.g. 10-50 mg, such as 10-40 mg, per day, the dosage being adapted to the patient and the patient's response. As mentioned above, the treatment should often be started with a low dosage and then increased until the suitable dosage has been established. The dosage of galanthamine functional equivalents or galanthamine derivatives is expressed as the equipotent amount of galanthamine hydrobromide, the reference basis being the capability of inhibiting acetylcholinesterase in the Thomsen et al. in vitro test mentioned above.

[0042] Examples of parenteral administration ranges are 0.1-1000 mg per day, such as 5-1000 mg per day, e.g. 10-500 mg per day, including 50-300 mg per day; lower dosages are often preferred, such as 10-50 mg per day, e.g. 10-30 mg per day.

[0043] For the oral administration, galanthamine or a galanthamine salt or derivative or- a functional equivalent may be formulated, for example, as an aqueous suspension or a solution in aqueous ethanol or as a solid composition such as a tablet or capsule. Suspensions or solutions for oral administration are typically of a concentration of 1-50 mg/ml, more commonly 5-40 mg/ml, for example, 10-40 mg/ml, typically 20-30 mg/ml of galanthamine. Divided doses into the range 0.5-5 mg/kg body weight per day are useful, in some situations divided doses in the range of 0,1-3 mg/kg body weight per day may also prove useful. Examples of dosages are up to 2000 mg per day, such as 0.1-2000 mg per day, or 5-2000 mg per day. Other ranges that should be mentioned are 100-600 mg per day or 10-500 mg per day, such as 10-50 or 10-30 mg per day. Typically, one might administer a dosage of 20-100 mg per day to a patient of a body weight of 40-100 kg, although in appropriate cases such dosages may prove useful for patients having a body weight outside this range. However, in other instances dosages of 50-300 mg per day to a patient of a body weight of 40-100 kg may be also be very useful. In other cases, dosages as low as 10 mg and as high as 200 mg may be appropriate for persons in this body weight range.

[0044] Galanthamine and its acid addition salts form crystals. They are generally only sparingly soluble in water at room temperature; therefore, injectable compositions are normally in the form of an aqueous suspension. If necessary, pharmaceutically-acceptable suspension aids may be employed. Typically, such a suspension will be employed at a concentration of 0.1-50 mg/ml, such as 1-50 mg/ml, more commonly 5-40 mg/ml, for example, 5-30 mg/ml or 10-40

mg/ml, such as 10-30 mg/ml, especially 20-30 mg/ml of galanthamine. As mentioned above, typical dosage rates when administering galanthamine by injection are the range 0.01-20 mg per day depending upon the patient. For example, divided doses in the range 0,5-5 mg/kg body weight per day may prove useful. Typically, one might administer a dosage of 5-50 mg per day to a patient of a body weight of 40-100 kg, although in appropriate cases such dosages may prove useful for patients having a body weight outside this range. In other cases, dosages as low as 5 mg and as high as 200 mg per day may be appropriate for persons in this body weight range.

[0045] Galanthamine and its pharmaceutically acceptable acid addition salts, and its derivatives and functional equivalents, when suited therefor, may be administered by subcutaneous, intravenous or intramuscular injection.

[0046] The parenteral dosage rate of galanthamine can also be expressed by reference to the body weight of the patient; in this case, a normal dosage rate will often be 0.1 to 4 mg/kg body weight. Depot compositions will often deliver a dosage rate of 0.01 to 5.0 mg/kg per day.

[0047] In preparing tablets or capsules, standard tablet or capsule-making techniques may be employed. If desired, a pharmaceutically acceptable carrier such as starch or lactose may be used in preparing galanthamine or galanthamine equivalent tablets. Capsules may be prepared using soft gelatine as the encapsulating agent. If desired, such capsules may be in the form of sustained release capsules wherein the main capsule contains microcapsules of galanthamine or functional equivalents thereof which release the contents over a period of several hours thereby maintaining a constant level of galanthamine or its functional equivalent in the patient's blood.

[0048] The following specific formulations may find use according to the invention:

[0049] Tablets or capsules containing 0.1, 1, 2, 5, 10 and 25 mg galantahamine hydrobromide or functional equivalent to be taken four times a day, or a sustained-release preparation delivering an equivalent daily dose.

[0050] Liquid formulation for oral administration available in 5 mg/ml and 25 mg/ml concentration.

[0051] Other interesting administration forms of galanthamine and functional equivalents are suppositories, a slow-release plaster, and other depot compositions.

[0052] All of the above-mentioned administration forms are prepared in manners known per se.

[0053] Although galanthamine must be considered as having a high degree of safety, there have been certain side effects in a few of the patients treated. These have been slight nausea in about 30% of the cases (the nausea, however, disappearing after about one week of treatment), vomiting and dizziness in 5-10% of the patients (also disappearing after about one week of treatment in most cases), and more severe side effects in 4-6% of the patients. These more severe side effects must be considered acceptable in view of the effect of the drug; however, in patients who are suspected of developing arrhythmia, it should be considered to administer, e.g., atropine in combination with the treatment according to the invention. -

[0054] In situations where the cholinesterase inhibitor may be given simultaneously with a benzodiazepine a pharmaceutical composition comprising both the cholinesterase inhibitor and the benzodiazepine.

[0055] The administration forms for the cholinesterase inhibitors, galanthamine, the galanthamine salts and the galanthamine derivatives may be orally and parenterally. The administration being dependent on the patient's age and weight, and on the daily life of the patient as well as the severity of the disease.

[0056] Parenteral administration may comprise suitable injection, e.g. intravenous, intramuscular, subcutaneous, as well as transdermal or rectally administration or implantation of e.g. suitable delivery devices, such as a intrathetical device.

[0057] Formulations for parenteral use may be a solution or suspension, a plaster for transdermal application, or a suppository.

EXAMPLE 1

Test for cholinesterase activity in blood samples

Method

[0058] SIGMA DIAGNOSTICS® CHOLINESTERASE (PTC) kit, available from Sigma Diagnostics, can be used for determining the activity and selectivity of cholinesterase inhibitors. In the following, it is illustrated how the kit is used for the determination of the activity and selectivity of Nivalin (Galanthamine hydrobromide).

[0059] Reactions involved in the cholinesterase assay are as follows:

$$\text{Propionylthiocholine} + H_2O \xrightarrow{\text{esterase}} \text{Propionic Acid} + \text{Thio choline Thiocholine} + \text{5,5'-Dithiobis-2-Nitrobenzoic Acid} \rightarrow \text{5-Thio-2-Nitrobenzoic Acid}$$

[0060] 5-Thio-2-Nitrobenzoic Acid is assessed by measuring the absorbance at 405 nm. The rate of change in absorbance at 405 nm is directly proportional to cholinesterase activity.

[0061] The activity of erythrocyte cholinesterase may be calculated on the basis of the measurement of butyrylcholinesterase (pseudocholinesterase) in serum and cholinesterase in hemolyzed whole blood (hemolysate), both measured simultaneously by the method described above, and evaluated according to the hematocrit value according to the formula

$$HChE = (EChE \times Hct^*) + (PChE \times (1-Hct^*))$$

$$\text{Therefore, } EChE = \frac{HChE - (PChE \times (1-Hct^*))}{Hct^*}$$

* Hematocrit value expressed as decimal equivalent (i.e., 44% = 0.44.

[0062] In the above formulae, EChE is erythrocyte cholinesterase activity, PChE is plasma cholinesterase activity, HChE is hemolysate cholinesterase activity, and Hct is hematocrit value of the sample.

[0063] Another way of assessing the cholinesterase activity is to measure the plasma cholinesterase and the cholinesterase in purified hemolyzed erythrocytes. By doing this, the values are obtained directly.

[0064] Blood samples from 3 patients were tested with the Sigma test. The tests were carried out with samples where no Nivalin was added and with samples where 1.25 µg/ml Nivalin and 2.5 µg/ml were added in vitro. The results are shown below in table 1.1.

Table 1.1

Nivalin added µg/ml	Hemolysate ChE activity	Serum ChE activity
0	1.00	1.00
1.25	0.96	0.98
2.50	0.86	0.97

[0065] The results show a significant reduction of the hemolysate cholinesterase activity with increased concentration of galanthamine hydrobromide, whereas the data for the serum activity do not show any statistically significant change as a response to the addition of the galanthamine hydrobromide, which is an indication of a high selectivity of the galanthamine hydrobromide with respect to acetylcholinesterase as opposed to butyrylcholinesterase. Selectivity for acetylcholinesterase in erythrocytes opposed to butyrylcholinesterase is contemplated to reflect the selectivity for acetylcholinesterase at nicotinic receptor sites opposed to the acetylcholinesterase at muscarinic receptor sites.

[0066] This test may be used as a screening for candidate cholinesterase inhibitors with respect to their selectivity.

EXAMPLE 2

Formulations of tablets containing galanthamine

[0067]

Composition of 1 tablet containing 1 mg galanthamine	
Galanthamine hydrobromide	0.001 g
Calcium phosphate	0.032 g
Lactose	0.005 g
Wheat Starch	0.0056 g
Microcrystalline Cellulose	0.015 g
Talc	0.0007 g
Magnesium Stearate	0.0007 g
Composition of 1 tablet containing 5 mg galanthamine	
Galanthamine hydrobromide	0.005 g
Calcium phosphate	0.024 g
Lactose	0.004 g
Wheat Starch	0.004 g
Microcrystalline Cellulose	0.04 g
Talc	0.002 g
Magnesium Stearate	0.001 g
Composition of 1 tablet containing 10 mg galanthamine	
Galanthamine hydrobromide	0.010 g
Lactose	0.040 g
Wheat Starch	0.0234 g
Microcrystalline Cellulose	0.0374 g
Talc	0.0036 g
Magnesium Stearate	0.0012 g
Gelatin	0.0044 g

Preparation

[0068] All the tablets are prepared according to routine tabletting procedures.

EXAMPLE 3

Auditory brain stem response

Methods

[0069] Electrical potentials caused by click-stimulation in the ears are measured with electrodes positioned outside

on the head of the examined person. In the configuration of the potentials are components from the brain stem and the brain.

Persons

[0070] A patient suffering from bipolar manic-depression in the depressive state and a healthy person, respectively.

Drug

[0071] Tablet containing 10 mg galanthamine

Results

[0072] Figures 1A, 1B, 2A and 2B show the potentials from a depressive patient and a healthy person, both treated and untreated.

[0073] Figures 1A, and 2A show that in the depressed patient, the auditory brain stem response without treatment has a much smaller, almost half, amplitude of the potential compared to the amplitude of the untreated healthy person.

[0074] Furthermore, figures 1A and 1B show a dramatically increase of the amplitude in the treated depressive patient compared to untreated persons.

[0075] Also, from figures 2A and 2B it is seen that the potentials do not change from the untreated person to the treated person.

Conclusion.

[0076] From the results in the depressed person it is seen that the potentials change after treatment with galanthamine, such as explained above. This means that galanthamine must be able to cross the blood-brain barrier, since it is possible to inhibit in synapses in the brain stem, which is positioned on the "brain side" of the blood-brain barrier.

LEGENDS TO FIGURES

[0077]

Fig. 1 A shows the auditory evoked response of a depressed patient (a manic depressed patient in the depressed state) without treatment with galanthamine.

Fig. 1 B shows the auditory evoked response of a depressed patient (the same as in fig. 1 A) 2 hours after treatment with 10 mg of galanthamine.

Fig. 2 A shows the auditory evoked response of a healthy person without treatment with galanthamine.

Fig. 2 B shows the auditory evoked response of a healthy person (the same as in fig. 2 A) 2 hours after treatment with 10 mg of galanthamine.

Claims

1. The use of a pharmaceutically acceptable cholinesterase inhibitor or a prodrug therefor for the preparation of a pharmaceutical composition for the treatment of schizophrenia, in particular affective or schizoaffective type schizophrenia.

2. The use according to claim 1, wherein the cholinesterase inhibitor is used as the sole or main drug in the treatment.

3. The use according to claim 1 or claim 2 wherein the cholinesterase inhibitor is selected from the group consisting of physostigmine, tacrine and tacrine analogues, galanthamine, epigalanthamine, norgalanthamine, fasciculin, metrifonate, heptylphysostigmine, norpyridostigmine, norneostigmine, and huperzine, and prodrugs therefor.

4. The use according to any one of the preceding claims, wherein the cholinesterase inhibitor is an acetylcholinesterase inhibitor active substantially selectively at nicotinic receptor sites.

5. The use according to claim 4, wherein the acetylcholinesterase inhibitor is one which has an at least 10-fold selectivity for acetylcholinesterase as opposed to butyrylcholinesterase.

6. The use according to claim 5, wherein the acetylcholinesterase inhibitor is one which has an at least 20-fold selectivity for acetylcholinesterase as opposed to butyrylcholinesterase.

7. The use according to claim 6, wherein the acetylcholinesterase inhibitor is one which has an at least 40-fold selectivity for acetylcholinesterase as opposed to butyrylcholinesterase.

8. The use according to any of the preceding claims, wherein the acetylcholinesterase inhibitor is one which, upon administration in an amount of 10 mg to a healthy adult, results in inhibition of at least 40% of the acetylcholinesterase activity in erythrocytes from the adult and no substantial inhibition of butyrylcholinesterase therein.

9. The use according to claim 8, wherein the acetylcholinesterase inhibitor is one which, when administered in an amount of 10 mg to an adult, results in inhibition of at least 50% of the acetylcholinesterase activity in erythrocytes from the adult.

10. The use according to any of the preceding claims, wherein the acetylcholinesterase inhibitor is one which is able to cross the blood brain barrier in humans.

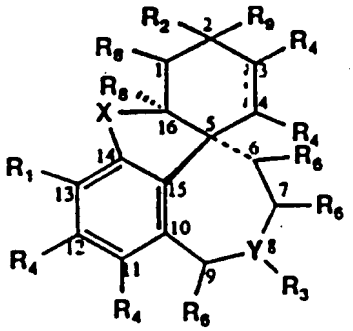
11. The use according to any of the preceding claims, in which the cholinesterase inhibitor is one which, upon administration to a human, increases the cortisol level.

12. The use according to claim 1 wherein the cholinesterase inhibitor is galanthamine or a salt or derivative thereof.

13. The use of galanthamine or a galanthamine salt or a galanthamine derivative for the preparation of a pharmaceutical composition for treating schizophrenia, in particular affective or schizoaffective type schizophrenia.

14. The use according to claim 13, wherein the cholinesterase inhibitor is used as the sole or main drug in the treatment.

15. The use according to any of claims 12 to 14, in which the compound is a galanthamine derivative of the general formula II



II

wherein the broken line represents an optionally present double bond between carbon atoms 3 and 4, R_1 and R_2 are each selected independently from the group consisting of hydrogen, hydroxyl, amino or alkylamino, cyano, sulfhydryl, alkoxy of 1-6 carbon atoms, alkylthio, aryloxy, arylthio, R_5-substituted aryloxy, R_5-substituted arylthio, aralkoxy, an aliphatic or aryl carbamyl group wherein the aliphatic or aryl moiety may be R_5 substituted or unsubstituted, aralkylthio, R_5-substituted aralkoxy, R_5-substituted aralkylthio, aryloxymethyl, R_5-substituted aryloxymethyl, alkanoyloxy, hydroxy-substituted alkanoyloxy, benzoyloxy, R_5-substituted benzoyloxy, aryloxy-

carbonyl and R_5-substituted aryloxycarbonyl, R_1 may also be alkyl of up to 14 carbon atoms, or hydroxymethyl, R_2 may also be carboxymethyl, provided that at least one of R_1 and R_2 is hydroxy, amino or alkylamino unless R_8 is hydroxymethyl,

R_3 is hydrogen, straight or branched chain alkyl of 1-6 carbon atoms, cycloalkylmethyl, phenyl, R_5-substituted phenyl, alkylphenyl, R_5-substituted alkylphenyl, heterocyclyl selected from α- or β-furyl, α- or β-thienyl or thenyl, pyridyl, pyrazinyl, and pyrimidyl, alkyl-hetero-cyclyl or R'-substituted heterocyclyl, where R' is alkyl or alkoxy,

each R_4 is independently selected from hydrogen, hydroxyl, sulfhydryl, alkyl, aryl, aralkyl, alkoxy, mercaptoalkyl, aryloxy, thiaryloxy, alkaryloxy, mercarptoalkaryl, nitro, amino, N-alkylamino, N-arylamino, N-alkarylamino, fluoro, chloro, bromo, iodo, and trifluoromethyl,

R_5 is selected from the same groups as R_4,

R_6 is hydrogen, halo, trifluoromethyl or alkyl of 1 to 4 carbon atoms, with the proviso that when R_6 is in position 7 or 9, it is not halo,

R_8 is hydrogen or hydroxymethyl,

R_9 is hydrogen or alkyl of 1 to 6 carbon atoms, or when R_2 is hydroxyl, R_9 may be a moiety of formula II wherein R_9 is hydrogen and R_2 is a linking bond; or

R_2 and R_9 may jointly form semicarbazone,

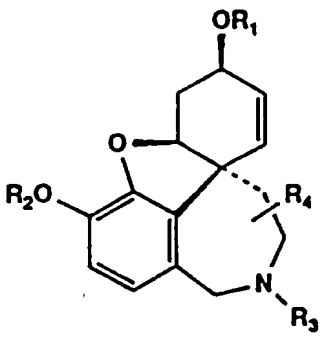
X is oxygen or NR_5,

Y is nitrogen or phosphorus,

and methylenedioxy derivatives thereof with the proviso that when X is O, R_3 is not methyl when R_1 is methoxy, R_2 is hydroxy, and all R_4 are hydrogen,

or a pharmaceutically acceptable acid addition salt thereof.

16. The use according to any of claims 12-14, in which the galanthamine derivative is a compound of the formula I



I

wherein R^1 and R^2 which may be the same or different each represents a hydrogen atom or an acyl group, such as a lower alkanoyl group, e.g. an acetyl group or a straight-chained or branched alkyl group, e.g. methyl, ethyl, propyl, or isopropyl;

R^3 is a straight or branched chain alkyl, alkenyl or alkaryl group which is optionally substituted by a halogen

atom or a cycloalkyl, hydroxy, alkoxy, nitro, amino, aminoalkyl, acylamino, heteroaryl, heteroarylalkyl, aroyl, aroylalkyl or cyano group; and

R^4 represents a hydrogen or a halogen atom attached to at least one of the ring carbons of the tetracyclic skeleton, with the proviso that when R_4 is in a position neighboring the nitrogen atom then R_4 is different from halogen,

or a pharmaceutically acceptable salt thereof, such as a hydrobromide, hydrochloride, methylsulphate or methiodide.

17. The use according to any of claims 12-16, wherein galanthamine hydrobromide is used.

18. The use according to any of claims 12 to 17, wherein the galanthamine derivative is one which is able to cross the blood brain barrier in humans.

19. The use according to any of claims 1 to 18, wherein the pharmaceutical composition is a tablet, a capsule, a sustained release capsule comprising micro capsules of the active ingredient, a solution or suspension, a plaster for transdermal application, or a suppository.

20. The use according to any of the preceding claims, wherein the cholinesterase inhibitor or the galanthamine or the galanthamine derivative is administered parenterally at a dosage which is equipotent with 0.1-1,000 mg of galanthamine hydrobromide per day, such as 5-1,000 mg of galanthamine hydrobromide per day.

21. The use according to claim 20, wherein the dosage is equipotent with 10-500 mg galanthamine hydrobromide per day, such as 50-300 mg per day.

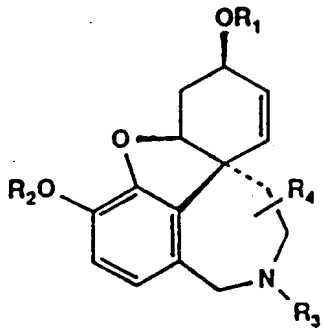
22. The use according to claim 21, wherein the dosage is equipotent with 10-50, in particular 10-30, mg galanthamine hydrobromide per day.

23. The use according to any of claims 1-19, wherein the cholinesterase inhibitor or the galanthamine or the galanthamine derivative is administered orally at a dosage which is equipotent with 0.1-2000 mg galanthamine hydrobromide per day, such as 5-2000 mg galanthamine hydrobromide per day.

24. The use according to claim 23, wherein the dosage is equipotent with 10-500 mg galanthamine hydrobromide per day.

25. The use according to claim 24, wherein the dosage is equipotent with 10-50 mg, such as 10-30 mg, of galanthamine hydrobromide per day.

26. The use of a compound of formula I



I

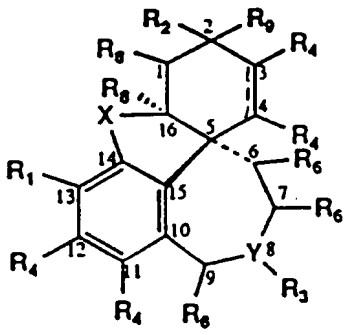
wherein R^1 and R^2 which may be the same or different each represents a hydrogen atom or an acyl group, such as a lower alkanoyl group, e.g. an acetyl group or a straight-chained or branched alkyl group, e.g. methyl, ethyl, propyl, or isopropyl;

R^3 is a straight or branched chain alkyl, alkenyl or alkaryl group which is optionally substituted by a halogen atom or a cycloalkyl, hydroxy, alkoxy, nitro, amino, aminoalkyl, acylamino, heteroaryl, heteroarylalkyl, aroyl, aroylalkyl or cyano group; and

R^4 represents a hydrogen or a halogen atom attached to at least one of the ring carbons of the tetracyclic skeleton, with the proviso that when R_4 is in a position neighboring the nitrogen atom then R_4 is different from halogen,

or a pharmaceutically acceptable salt thereof, such as a hydrobromide, hydrochloride, methylsulphate or methiodide in the manufacture of a pharmaceutical preparation for the treatment of schizophrenia.

27. The use of a compound of formula II



II

wherein the broken line represents an optionally present double bond between carbon atoms 3 and 4, R_1 and R_2 are each selected independently from the group consisting of hydrogen, hydroxyl, amino or alkylamino, cyano, sulfhydryl, alkoxy of 1-6 carbon atoms, alkylthio, aryloxy, arylthio, R_5-substituted aryloxy, R_5-substituted arylthio, aralkoxy, an aliphatic or aryl carbamyl group wherein the aliphatic or aryl moiety may be R_5 substituted or unsubstituted, aralkylthio, R_5-substituted aralkoxy, R_5-substituted aralkylthio, aryloxymethyl, R_5-substituted aryloxymethyl, alkanoyloxy, hydroxysubstituted alkanoyloxy, benzoyloxy, R_5-substituted benzoyloxy, aryloxycarbonyl and R_5-substituted aryloxycarbonyl, R_1 may also be alkyl of up to 14 carbon atoms, or hydroxymethyl, R_2 may also be carboxymethyl, provided that at least one of R_1 and R_2 is hydroxy, amino or alkylamino unless R_8 is hydroxymethyl,

R_3 is hydrogen, straight or branched chain alkyl of 1-6 carbon atoms, cycloalkylmethyl, phenyl, R_5-substituted phenyl, alkylphenyl, R_5-substituted alkylphenyl, heterocyclyl selected from α- or β-furyl, α- or β-thienyl or thenyl, pyridyl, pyrazinyl, and pyrimidyl, alkyl-hetero-cyclyl or R'-substituted heterocyclyl, where R' is alkyl or alkoxy,

each R_4 is independently selected from hydrogen, hydroxyl, sulfhydryl, alkyl, aryl, aralkyl, alkoxy, mercaptoalkyl, aryloxy, thiaryloxy, alkaryloxy, mercarptoalkaryl, nitro, amino, N-alkylamino, N-arylamino, N-alkarylamino, fluoro, chloro, bromo, iodo, and trifluoromethyl,

R_5 is selected from the same groups as R_4,

R_6 is hydrogen, halo, trifluoromethyl or alkyl of 1 to 4 carbon atoms, with the proviso that when R_6 is in position 7 or 9, it is not halo,

R_8 is hydrogen or hydroxymethyl,

R_9 is hydrogen or alkyl of 1 to 6 carbon atoms, or when R_2 is hydroxyl, R_9 may be a moiety of formula II wherein R_9 is hydrogen and R_2 is a linking bond; or

R_2 and R_9 may jointly form semicarbazone,

X is oxygen or NR_5,

Y is nitrogen or phosphorus,

and methylenedioxy derivatives thereof with the proviso that when X is O, R_3 is not methyl when R_1 is methoxy, R_2 is hydroxy, and all R_4 are hydrogen,

or a pharmaceutically acceptable acid addition salt thereof in the manufacture of a pharmaceutical preparation for the treatment of schizophrenia.

Patentansprüche

1. Verwendung eines pharmazeutisch annehmbaren Cholinesterase-Inhibitors oder einer Prodrug dafür zur Herstellung einer pharmazeutischen Zusammensetzung zur Behandlung von Schizophrenie, insbesondere Schizophrenie des affektiven oder schizoaffektiven Typs.

2. Verwendung nach Anspruch 1, worin der Cholinesterase-Inhibitor als einziges Medikament oder als Hauptmedikament in der Behandlung eingesetzt wird.

3. Verwendung nach Anspruch 1 oder Anspruch 2, worin der Cholinesterase-Inhibitor aus der Gruppe bestehend aus Physostigmin, Tacrin und Tacrin-Analoga, Galanthamin, Epigalanthamin, Norgalanthamin, Fasciculin, Metrifonat, Heptylphysostigmin, Norpyridostigmin, Nomeostigmin und Huperzin und Prodrugs dafür ausgewählt ist.

4. Verwendung nach irgendeinem der vorhergehenden Ansprüche, worin der Cholinesterase-Inhibitor ein Acetylcholinesterase-Inhibitor mit im wesentlichen selektiver Aktivität an nikotinergen Rezeptorstellen ist.

5. Verwendung nach Anspruch 4, worin der Acetylcholinesterase-Inhibitor ein Inhibitor ist, der eine mindestens 10fache Selektivität für Acetylcholinesterase gegenüber Butyrylcholinesterase aufweist.

6. Verwendung nach Anspruch 5, worin der Acetylcholinesterase-Inhibitor ein Inhibitor ist, der eine mindestens 20fache Selektivität für Acetylcholinesterase gegenüber Butyrylcholinesterase aufweist.

7. Verwendung nach Anspruch 6, worin der Acetylcholinesterase-Inhibitor ein Inhibitor ist, der eine mindestens 40fache Selektivität für Acetylcholinesterase gegenüber Butyrylcholinesterase aufweist.

8. Verwendung nach irgendeinem der vorhergehenden Ansprüche, worin der Acetylcholinesterase-Inhibitor ein Inhibitor ist, welcher nach Verabreichung in einer Menge von 10 mg an einen gesunden Erwachsenen zu einer Inhibierung von mindestens 40% der Acetylcholinesterase-Aktivität in Erythrozyten des Erwachsenen und zu keiner wesentlichen Inhibierung der darin enthaltenden Butyrylcholinesterase führt.

9. Verwendung nach Anspruch 8, worin der Acetylcholinesterase-Inhibitor ein Inhibitor ist, welcher nach Verabreichung in einer Menge von 10 mg an einen Erwachsenen zu einer Inhibierung von mindestens 50% der Acetylcholinesterase-Aktivität in Erythrozyten des Erwachsenen führt.

10. Verwendung nach irgendeinem der vorhergehenden Ansprüche, worin der Acetylcholinesterase-Inhibitor ein Inhibitor ist, welcher in der Lage ist, die Blut-Hirn-Schranke bei Menschen zu passieren.

11. Verwendung nach irgendeinem der vorhergehenden Ansprüche, worin der Cholinesterase-Inhibitor ein Inhibitor ist, welcher nach Verabreichung an einen Menschen den Cortisolspiegel erhöht.

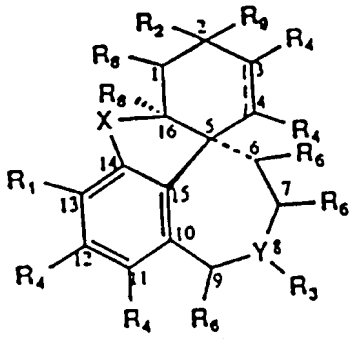
12. Verwendung nach Anspruch 1, worin der Cholinesterase-Inhibitor Galanthamin oder ein Salz oder Derivat davon

ist.

13. Verwendung von Galanthamin oder einem Galanthamin-Salz oder Galanthamin-Derivat zur Herstellung einer pharmazeutischen Zusammensetzung zur Behandlung von Schizophrenie, insbesondere Schizophrenie des affektiven oder schizoaffektiven Typs.

14. Verwendung nach Anspruch 13, worin der Cholinesterase-Inhibitor als einziges Medikament oder als Hauptmedikament in der Behandlung eingesetzt wird.

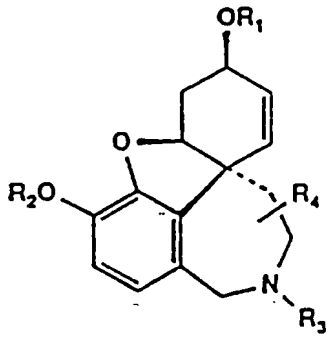
15. Verwendung nach irgendeinem der Ansprüche 12 bis 14, worin die Verbindung ein Galanthamin-Derivat der allgemeinen Formel II ist



II

worin die gestrichelte Linie eine gegebenenfalls vorhandene Doppelbindung zwischen den Kohlenstoffatomen 3 und 4 darstellt, R_1 und R_2 jeweils unabhängig aus der Gruppe bestehend aus Wasserstoff, Hydroxyl, Amino oder Alkylamino, Cyano, Sulfhydryl, Alkoxy mit 1-6 Kohlenstoffatomen, Alkylthio, Aryloxy, Arylthio, R_5 -substituiertem Aryloxy, R_5 -substituiertem Arylthio, Aralkoxy, einer aliphatischen oder Aryl-Carbamylgruppe, worin die aliphatische oder Arylgruppierung R_5-substituiert oder unsubstituiert sein kann, Aralkylthio, R_5-substituiertem Aralkoxy, R_5-substituiertem Aralkylthio, Aryloxymethyl, R_5-substituiertem Aryloxymethyl, Alkanoyloxy, hydroxysubstituiertem Alkanoyloxy, Benzoyloxy, R_5-substituiertem Benzoyloxy, Aryloxycarbonyl und R_5-substituiertem Aryloxycarbonyl ausgewählt sind, R_1 auch Alkyl mit bis zu 14 Kohlenstoffatomen oder Hydroxymethyl sein kann, R_2 auch Carboxymethyl sein kann, vorausgesetzt, daß mindestens eines von R_1 und R_2 Hydroxy, Amino oder Alkylamino ist, wenn R_8 nicht Hydroxymethyl ist,
R_3 Wasserstoff, geradkettiges oder verzweigtkettiges Alkyl mit 1-6 Kohlenstoffatomen, Cycloalkylmethyl, Phenyl, R_5-substituiertes Phenyl, Alkylphenyl, R_5-substituiertes Alkylphenyl, Heterocyclyl, ausgewählt aus α- oder β-Furyl, α- oder β-Thienyl oder -Thenyl, Pyridyl, Pyrazinyl und Pyrimidyl, Alkylheterocyclyl oder R' -substituiertes Heterocyclyl, wobei R' Alkyl oder Alkoxy ist, darstellt,
jedes R_4 unabhängig aus Wasserstoff, Hydroxyl, Sulfhydryl, Alkyl, Aryl, Aralkyl, Alkoxy, Mercaptoalkyl, Aryloxy, Thiaryloxy, Alkaryloxy, Mercaptoalkaryl, Nitro, Amino, N-Alkylamino, N-Arylamino, N-Alkarylamino, Fluor, Chlor, Brom, Iod und Trifluormethyl ausgewählt ist,
R_5 aus den gleichen Gruppen wie R_4 ausgewählt ist,
R_6 Wasserstoff, Halogen, Trifluormethyl oder Alkyl mit 1 bis 4 Kohlenstoffatomen ist, mit der Maßgabe, daß, wenn R_6 in Position 7 oder 9 vorliegt, es kein Halogen ist,
R_8 Wasserstoff oder Hydroxymethyl ist,
R_9 Wasserstoff oder Alkyl mit 1 bis 6 Kohlenstoffatomen ist oder, wenn R_2 Hydroxyl ist, R_9 eine Gruppierung der Formel II sein kann, worin R_9 Wasserstoff ist und R_2 eine verknüpfende Bindung ist; oder
R_2 und R_9 zusammen Semicarbazon bilden können,
X Sauerstoff oder NR_5 ist,
Y Stickstoff oder Phosphor ist,
oder ein Methylendioxy-Derivat davon, mit der Maßgabe, daß, wenn X O ist, R_3 nicht Methyl ist, wenn R_1 Methoxy ist, R_2 Hydroxy ist und alle R_4 Wasserstoff sind,
oder ein pharmazeutisch annehmbares Säureadditionssalz davon.

16. Verwendung nach irgendeinem der Ansprüche 12-14, worin das Galanthamin-Derivat eine Verbindung der Formel I ist



I

worin R^1 und R^2, die gleich oder verschieden sein können, jeweils ein Wasserstoffatom oder eine Acylgruppe, wie z.B. eine niedere Alkanoylgruppe, z.B. eine Acetylgruppe, oder eine geradkettige oder verzweigte Alkylgruppe, z.B. Methyl, Ethyl, Propyl oder Isopropyl, darstellen;
R^3 eine geradkettige oder verzweigtkettige Alkyl-, Alkenyl- oder Alkarylgruppe ist, welche gegebenenfalls durch ein Halogenatom oder eine Cycloalkyl-, Hydroxy-, Alkoxy-, Nitro-, Amino-, Aminoalkyl-, Acylamino-, Heteroaryl-, Heteroarylalkyl-, Aroyl-, Aroylalkyl- oder Cyanogruppe substituiert ist; und
R^4 ein Wasserstoff- oder Halogenatom darstellt, das mit mindestens einem der Ringkohlenstoffatome des tetracyclischen Gerüsts verknüpft ist, mit der Maßgabe, daß, wenn R^4 in einer Nachbarposition zum Stickstoffatom vorliegt, R^4 kein Halogen ist,
oder ein pharmazeutisch annehmbares Salz davon, wie z.B. ein Hydrobromid, Hydrochlorid, Methylsulfat oder Methiodid.

17. Verwendung nach irgendeinem der Ansprüche 12-16, worin Galanthamin-Hydrobromid verwendet wird.

18. Verwendung nach irgendeinem der Ansprüche 12 bis 17, worin das Galanthamin-Derivat ein Derivat ist, welches in der Lage ist, die Blut-Hirn-Schranke bei Menschen zu passieren.

19. Verwendung nach irgendeinem der Ansprüche 1 bis 18, worin die pharmazeutische Zusammensetzung eine Tablette, eine Kapsel, eine Kapsel zur verzögerten Freisetzung, die Mikrokapseln des aktiven Bestandteils umfaßt, eine Lösung oder Suspension, ein Pflaster für transdermale Applikation oder ein Zäpfchen ist.

20. Verwendung nach irgendeinem der vorhergehenden Ansprüche, worin der Cholinesterase-Inhibitor oder das Galanthamin oder das Galanthamin-Derivat parenteral in einer Dosis verabreicht wird, welche dieselbe Wirkung hat wie 0,1-1000 mg Galanthamin-Hydrobromid pro Tag, z.B. 5-1000 mg Galanthamin-Hydrobromid pro Tag.

21. Verwendung nach Anspruch 20, worin die Dosis dieselbe Wirkung hat wie 10-500 mg Galanthamin-Hydrobromid pro Tag, z.B. 50-300 mg pro Tag.

22. Verwendung nach Anspruch 21, worin die Dosis dieselbe Wirkung hat wie 10-50 mg, insbesondere 10-30 mg, Galanthamin-Hydrobromid pro Tag.

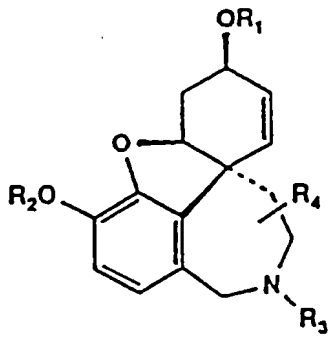
23. Verwendung nach irgendeinem der Ansprüche 1-19, worin der Cholinesterase-Inhibitor oder das Galanthamin oder das Galanthamin-Derivat oral in einer Dosis verabreicht wird, welche dieselbe Wirkung hat wie 0,1-2000 mg Galanthamin-Hydrobromid pro Tag, z.B. 5-2000 mg Galanthamin-Hydrobromid pro Tag.

24. Verwendung nach Anspruch 23, worin die Dosis dieselbe Wirkung hat wie 10-500 mg Galanthamin-Hydrobromid pro Tag.

25. Verwendung nach Anspruch 24, worin die Dosis dieselbe Wirkung hat wie 10-50 mg, z.B. 10-30 mg, Galanthamin-

Hydrobromid pro Tag.

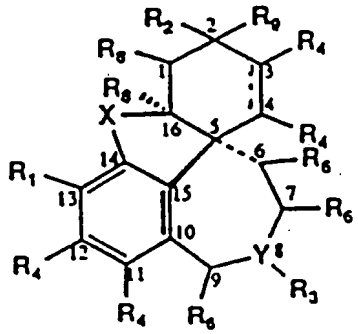
26. Verwendung einer Verbindung der Formel I



I

worin R^1 und R^2, die gleich oder verschieden sein können, jeweils ein Wasserstoffatom oder eine Acylgruppe, wie z.B. eine niedere Alkanoylgruppe, z.B. eine Acetylgruppe, oder eine geradkettige oder verzweigte Alkylgruppe, z.B. Methyl, Ethyl, Propyl oder Isopropyl, darstellen;
R^3 eine geradkettige oder verzweigtkettige Alkyl-, Alkenyl- oder Alkarylgruppe ist, welche gegebenenfalls durch ein Halogenatom oder eine Cycloalkyl-, Hydroxy-, Alkoxy-, Nitro-, Amino-, Aminoalkyl-, Acylamino-, Heteroaryl-, Heteroarylalkyl-, Aroyl-, Aroylalkyl- oder Cyanogruppe substituiert ist; und
R^4 ein Wasserstoff- oder Halogenatom darstellt, das mit mindestens einem der Ringkohlenstoffatome des tetracyclischen Gerüsts verknüpft ist, mit der Maßgabe, daß, wenn R^4 in einer Nachbarposition zum Stickstoffatom vorliegt, R^4 kein Halogen ist,
oder eines pharmazeutisch annehmbares Salzes davon, wie z.B. eines Hydrobromids, Hydrochlorids, Methylsulfats oder Methiodids, zur Herstellung eines pharmazeutischen Präparats zur Behandlung von Schizophrenie.

27. Verwendung einer Verbindung der Formel II



II

worin die gestrichelte Linie eine gegebenenfalls vorhandene Doppelbindung zwischen den Kohlenstoffatomen 3 und 4 darstellt, R_1 und R_2 jeweils unabhängig aus der Gruppe bestehend aus Wasserstoff, Hydroxyl, Amino oder Alkylamino, Cyano, Sulfhydryl, Alkoxy mit 1-6 Kohlenstoffatomen, Alkylthio, Aryloxy, Arylthio, R_5 -substituiertem Aryloxy, R_5 -substituiertem Arylthio, Aralkoxy, einer aliphatischen oder Aryl-Carbamylgruppe, worin die aliphatische oder Arylgruppierung R_5-substituiert oder unsubstituiert sein kann, Aralkylthio, R_5-substituiertem Aralkoxy, R_5-substituiertem Aralkylthio, Aryloxymethyl, R_5-substituiertem Aryloxymethyl, Alkanoyloxy,

hydroxysubstituiertem Alkanoyloxy, Benzoyloxy, R_5-substituiertem Benzoyloxy, Aryloxycarbonyl und R_5-substituiertem Aryloxycarbonyl ausgewählt sind, R_1 auch Alkyl mit bis zu 14 Kohlenstoffatomen oder Hydroxymethyl sein kann, R_2 auch Carboxymethyl sein kann, vorausgesetzt, daß mindestens eines von R_1 und R_2 Hydroxy, Amino oder Alkylamino ist, wenn R_8 nicht Hydroxymethyl ist,

R_3 Wasserstoff, geradkettiges oder verzweigtkettiges Alkyl mit 1-6 Kohlenstoffatomen, Cycloalkylmethyl, Phenyl, R_5-substituiertes Phenyl, Alkylphenyl, R_5-substituiertes Alkylphenyl, Heterocyclyl, ausgewählt aus α- oder β-Furyl, α- oder β-Thienyl oder -Thenyl, Pyridyl, Pyrazinyl und Pyrimidyl, Alkylheterocyclyl oder R' -substituiertes Heterocyclyl, wobei R' Alkyl oder Alkoxy ist, darstellt,

jedes R_4 unabhängig aus Wasserstoff, Hydroxyl, Sulfhydryl, Alkyl, Aryl, Aralkyl, Alkoxy, Mercaptoalkyl, Aryloxy, Thiaryloxy, Alkaryloxy, Mercaptoalkaryl, Nitro, Amino, N-Alkylamino, N-Arylamino, N-Alkarylamino, Fluor, Chlor, Brom, Iod und Trifluormethyl ausgewählt ist,

R_5 aus den gleichen Gruppen wie R_4 ausgewählt ist,

R_6 Wasserstoff, Halogen, Trifluormethyl oder Alkyl mit 1 bis 4 Kohlenstoffatomen ist, mit der Maßgabe, daß, wenn R_6 in Position 7 oder 9 vorliegt, es kein Halogen ist,

R_8 Wasserstoff oder Hydroxymethyl ist,

R_9 Wasserstoff oder Alkyl mit 1 bis 6 Kohlenstoffatomen ist oder, wenn R_2 Hydroxyl ist, R_9 eine Gruppierung der Formel II sein kann, worin R_9 Wasserstoff ist und R_2 eine verknüpfende Bindung ist; oder

R_2 und R_9 zusammen Semicarbazon bilden können,

X Sauerstoff oder NR_5 ist,

Y Stickstoff oder Phosphor ist,

oder von Methylendioxy-Derivaten davon, mit der Maßgabe, daß, wenn X O ist, R_3 nicht Methyl ist, wenn R_1 Methoxy ist, R_2 Hydroxy ist und alle R_4 Wasserstoff sind,

oder eines pharmazeutisch annehmbaren Säureadditionssalzes davon zur Herstellung eines pharmazeutischen Präparats zur Behandlung von Schizophrenie.

Revendications

1. Utilisation d'un inhibiteur de cholinestérase acceptable du point de vue pharmaceutique ou d'un bioprécurseur de celui-ci pour la préparation d'une composition pharmaceutique pour le traitement de la schizophrénie, en particulier de la schizophrénie de type affectif ou schizoaffectif.

2. Utilisation suivant la revendication 1, dans laquelle l'inhibiteur de cholinestérase est utilisé en tant que médicament unique ou principal dans le traitement.

3. Utilisation suivant les revendications 1 ou 2, dans laquelle l'inhibiteur de cholinestérase est choisi dans le groupe consistant en physostigmine, tacrine et analogues de tacrine, galanthamine, épigalanthamine, norgalanthamine, fasciculine, métrifonate, heptyl-physostigmine, norpyridostigmine, nornéostigmine et huperzine, ainsi que leurs bioprécurseurs.

4. Utilisation suivant l'une quelconque des revendications précédentes, dans laquelle l'inhibiteur de cholinestérase est un inhibiteur d'acétylcholinestérase actif de façon pratiquement sélective au niveau des sites des récepteurs nicotiniques.

5. Utilisation suivant la revendication 4, dans laquelle l'inhibiteur d'acétylcholinestérase est un inhibiteur dont la sélectivité pour l'acétylcholinestérase est d'au moins dix fois par rapport à la butyrylcholinestérase.

6. Utilisation suivant la revendication 5, dans laquelle l'inhibiteur d'acétylcholinestérase est un inhibiteur dont la sélectivité pour l'acétylcholinestérase est d'au moins vingt fois par rapport à la butyrylcholinestérase.

7. Utilisation suivant la revendication 6, dans laquelle l'inhibiteur d'acétylcholinestérase est un inhibiteur dont la sélectivité pour l'acétylcholinestérase est d'au moins quarante fois par rapport à la butyrylcholinestérase.

8. Utilisation suivant l'une quelconque des revendications précédentes, dans laquelle l'inhibiteur d'acétylcholinestérase est un inhibiteur qui, lorsqu'il est administré en une quantité de 10 mg à un adulte en bonne santé, aboutit à une inhibition d'au moins 40% de l'activité acétylcholinestérase dans les érythrocytes de l'adulte et à aucune inhibition notable de la butyrylcholinestérase dans ceux-ci.

9. Utilisation suivant la revendication 8, dans laquelle l'inhibiteur d'acétylcholinestérase est un inhibiteur qui, lorsqu'il

est administré en une quantité de 10 mg à un adulte, aboutit à une inhibition d'au moins 50% de l'activité acétylcholinestérase dans les érythrocytes de l'adulte.

10. Utilisation suivant l'une quelconque des revendications précédentes, dans laquelle l'inhibiteur d'acétylcholinestérase est un inhibiteur qui est capable de traverser la barrière hémato-encéphalique chez les humains.

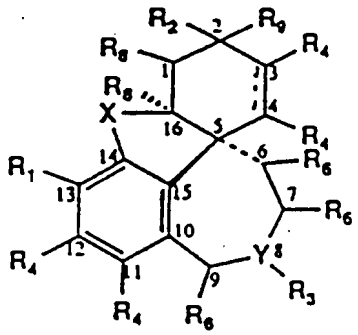
11. Utilisation suivant l'une quelconque des revendications précédentes, dans laquelle l'inhibiteur de cholinestérase est un inhibiteur qui, lorsqu'il est administré à un humain, augmente le taux de cortisol.

12. Utilisation suivant la revendication 1, dans laquelle l'inhibiteur de cholinestérase est la galanthamine ou un sel ou un dérivé de celle-ci.

13. Utilisation de galanthamine ou d'un sel de galanthamine ou d'un dérivé de galanthamine pour la préparation d'une composition pharmaceutique pour le traitement de la schizophrénie, en particulier la schizophrénie de type affectif ou schizoaffectif.

14. Utilisation suivant la revendication 13, dans laquelle l'inhibiteur de cholinestérase est utilisé en tant médicament unique ou principal dans le traitement.

15. Utilisation suivant l'une quelconque des revendications 12 à 14, dans laquelle le composé est un dérivé de galanthamine de formule générale II :



(II)

dans laquelle :

la ligne en pointillés représente une double liaison éventuellement présente entre les atomes de carbone 3 et 4,

R_1 et R_2 sont choisis chacun indépendamment dans le groupe consistant en atome d'hydrogène, groupe hydroxy, amino ou alkylamino, cyano, sulfhydryle, alcoxy ayant 1 à 6 atomes de carbone, alkylthio, aryloxy, arylthio, aryloxy substitué par R_5, arylthio substitué par R_5, aralcoxy, un groupe carbamoyle aliphatique ou aryle dans lequel la partie aliphatique ou aryle peut être substituée par R_5 ou non substituée, aralkylthio, aralcoxy substitué par R_5, aralkylthio substitué par R_5, aryloxyméthyle, aryloxyméthyle substitué par R_5, alcanoyloxy, alcanoyloxy substitué par un groupe hydroxy, benzoyloxy, benzoyloxy substitué par R_5, aryloxycarbonyle et aryloxycarbonyle substitué par R_5, R_1 peut être aussi un groupe alkyle ayant jusqu'à 14 atomes de carbone, ou un groupe hydroxyméthyle, R_2 peut aussi être un groupe carboxyméthyle, à condition qu'au moins l'un des R_1 et R_2 soit un groupe hydroxy, amino ou alkylamino à moins que R_8 ne soit un groupe hydroxyméthyle,

R_3 est un atome d'hydrogène, un groupe alkyle à chaîne droite ou ramifiée ayant 1 à 6 atomes de carbone, cycloalkylméthyle, phényle, phényle substitué par R_5, alkylphényle, alkylphényle substitué par R_5, hétérocyclyle choisi parmi les groupes α- ou β-furyle, α- ou β-thiényle ou thényle, pyridyle, pyrazinyle et pyrimidyle, alkylhétérocyclyle ou hétérocyclyle substitué par R', où R' est un groupe alkyle ou alcoxy,

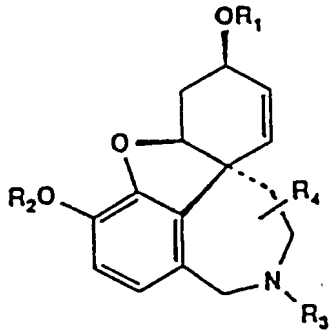
chaque R_4 est indépendamment choisi parmi un atome d'hydrogène, un groupe hydroxy, sulfhydryle, alkyle, aryle, aralkyle, alcoxy, mercaptoalkyle, aryloxy, thiaryloxy, alcaryloxy, mercaptoalcaryle, nitro, amino, N-alkylamino, N-arylamino, N-alcarylamino, fluoro, chloro, bromo, iodo et trifluorométhyle,

R_5 est choisi parmi les mêmes groupes que R_4,

R_6 est un atome d'hydrogène, un groupe halo, trifluorométhyle ou alkyle ayant 1 à 4 atomes de carbone, à con-

dition que lorsque R_6 est en position 7 ou 9, il ne soit pas un groupe halo,
R_8 est un atome d'hydrogène ou un groupe hydroxyméthyle,
R_9 est un atome d'hydrogène ou un groupe alkyle ayant 1 à 6 atomes de carbone, ou lorsque R_2 est un groupe hydroxy, R_9 peut être une partie de formule II dans laquelle R_9 est un atome d'hydrogène et R_2 est une liaison de réunion; ou
R_2 et R_9 peuvent former conjointement une semicarbazone,
X est un atome d'oxygène ou un groupe NR_5,
Y est un atome d'azote ou de phosphore,
et des dérivés méthylènedioxy de celui-ci à la condition que lorsque X est un atome d'oxygène, R_3 ne soit pas un groupe méthyle lorsque R_1 est un groupe méthoxy, R_2 soit un groupe hydroxy, et tous les R_4 soient un atome d'hydrogène, ou un sel d'addition d'acide de ceux-ci acceptable du point de vue pharmaceutique.

16. Utilisation suivant l'une quelconque des revendications 12 à 14, dans laquelle le dérivé de galanthamine est un composé de formule I :



(I)

dans laquelle :

R_1 et R_2 qui peuvent être identiques ou différents, représentent chacun un atome d'hydrogène, ou un groupe acyle, comme un groupe alcanoyle inférieur, par exemple, un groupe acétyle ou un groupe alkyle à chaîne droite ou ramifiée, par exemple, un groupe méthyle, éthyle, propyle ou isopropyle,
R_3 est un groupe alkyle, alcényle ou alcaryle à chaîne droite ou ramifiée qui est éventuellement substitué par un atome d'halogène ou un groupe cycloalkyle, hydroxy, alcoxy, nitro, amino, aminoalkyle, acylamino, hétéroaryle, hétéroarylalkyle, aroyle, aroylalkyle ou cyano, et
R_4 représente un atome d'hydrogène ou d'halogène attaché à au moins l'un des atomes de carbone de cycle du squelette tétracyclique, à la condition que lorsque R_4 se trouve en une position voisine de l'atome d'azote, alors R_4 soit différent d'un atome d'halogène,
ou un sel de celui-ci acceptable du point de vue pharmaceutique, comme un bromhydrate, un chlorhydrate, un méthylsulfate ou un méthiodure.

17. Utilisation suivant l'une quelconque des revendications 12 à 16, dans laquelle le bromhydrate de galanthamine est utilisé.

18. Utilisation suivant l'une quelconque des revendications 12 à 17, dans laquelle le dérivé de galanthamine est un dérivé qui est capable de traverser la barrière hémato-encéphalique chez les humains.

19. Utilisation suivant l'une quelconque des revendications 1 à 18, dans laquelle la composition pharmaceutique est un comprimé, une gélule, une gélule à libération continue comprenant des microgélules du composant actif, une solution ou une suspension, un emplâtre pour l'application transdermique, ou un suppositoire.

20. Utilisation suivant l'une quelconque des revendications précédentes dans laquelle l'inhibiteur de cholinestérase ou la galanthamine ou le dérivé de galanthamine est administré par voie parentérale à une dose qui est aussi efficace que 0,1 à 1000 mg de bromhydrate de galanthamine par jour, comme 5 à 1000 mg de bromhydrate de galanthamine par jour.

21. Utilisation suivant la revendication 20, dans laquelle la dose est aussi efficace que 10 à 500 mg de bromhydrate de galanthamine par jour, comme 50 à 300 mg par jour.

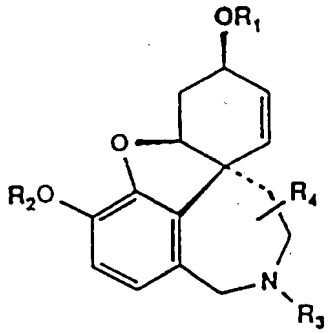
22. Utilisation suivant la revendication 21, dans laquelle la dose est aussi efficace que 10 à 50 mg, en particulier 10 à 30 mg de bromhydrate de galanthamine par jour.

23. Utilisation suivant l'une quelconque des revendications 1 à 19, dans laquelle l'inhibiteur de cholinestérase ou la galanthamine ou le dérivé de galanthamine est administré par voie orale à une dose qui est aussi efficace que 0,1 à 2000 mg de bromhydrate de galanthamine par jour, comme 5 à 2000 mg de bromhydrate de galanthamine par jour.

24. Utilisation suivant la revendication 23, dans laquelle la dose est aussi efficace que 10 à 500 mg de bromhydrate de galanthamine par jour.

25. Utilisation suivant la revendication 24, dans laquelle la dose est aussi efficace que 10 à 50 mg, comme 10 à 30 mg de bromhydrate de galanthamine par jour.

26. Utilisation d'un composé de formule I :

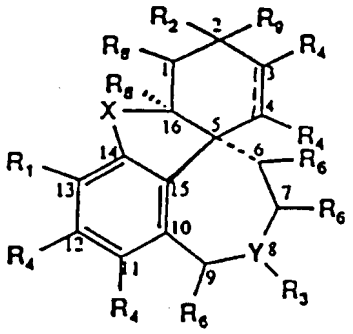


(I)

dans laquelle :

R_1 et R_2 qui peuvent être identiques ou différents, représentent chacun un atome d'hydrogène, ou un groupe acyle, comme un groupe alcanoyle inférieur, par exemple, un groupe acétyle ou un groupe alkyle à chaîne droite ou ramifiée, par exemple, un groupe méthyle, éthyle, propyle ou isopropyle,
R_3 est un groupe alkyle, alcényle ou alcaryle à chaîne droite ou ramifiée qui est éventuellement substitué par un atome d'halogène ou un groupe cycloalkyle, hydroxy, alcoxy, nitro, amino, aminoalkyle, acylamino, hétéroaryle, hétéroarylalkyle, aroyle, aroylalkyle ou cyano, et
R_4 représente un atome d'hydrogène ou d'halogène attaché à au moins l'un des atomes de carbone de cycle du squelette tétracyclique, à la condition que lorsque R_4 se trouve en une position voisine de l'atome d'azote, alors R_4 soit différent d'un atome d'halogène,
ou d'un sel de celui-ci acceptable du point de vue pharmaceutique, comme un bromhydrate, un chlorhydrate, un méthylsulfate ou un méthiodure, dans la fabrication d'une préparation pharmaceutique pour le traitement de la schizophrénie.

27. Utilisation d'un composé de formule II :



(II)

dans laquelle :

la ligne en pointillés représente une double liaison éventuellement présente entre les atomes de carbone 3 et 4,

R_1 et R_2 sont choisis chacun indépendamment dans le groupe consistant en atome d'hydrogène, groupe hydroxy, amino ou alkylamino, cyano, sulfhydryle, alcoxy ayant 1 à 6 atomes de carbone, alkylthio, aryloxy, arylthio, aryloxy substitué par R_5, arylthio substitué par R_5, aralcoxy, un groupe carbamoyle aliphatique ou aryle dans lequel la partie aliphatique ou aryle peut être substituée par R_5 ou non substituée, aralkylthio, aralcoxy substitué par R_5, aralkylthio substitué par R_5, aryloxyméthyle, aryloxyméthyle substitué par R_5, alcanoyloxy, alcanoyloxy substitué par un groupe hydroxy, benzoyloxy, benzoyloxy substitué par R_5, aryloxycarbonyle et aryloxycarbonyle substitué par R_5, R_1 peut être aussi un groupe alkyle ayant jusqu'à 14 atomes de carbone, ou un groupe hydroxyméthyle, R_2 peut aussi être un groupe carboxyméthyle, à condition qu'au moins l'un des R_1 et R_2 soit un groupe hydroxy, amino ou alkylamino à moins que R_8 ne soit un groupe hydroxyméthyle,

R_3 est un atome d'hydrogène, un groupe alkyle à chaîne droite ou ramifiée ayant 1 à 6 atomes de carbone, cycloalkylméthyle, phényle, phényle substitué par R_5, alkylphényle, alkylphényle substitué par R_5, hétérocyclyle choisi parmi les groupes α- ou β-furyle, α- ou β-thiényle ou thényle, pyridyle, pyrazinyle et pyrimidyle, alkylhétérocyclyle ou hétérocyclyle substitué par R', où R' est un groupe alkyle ou alcoxy,

chaque R_4 est indépendamment choisi parmi un atome d'hydrogène, un groupe hydroxy, sulfhydryle, alkyle, aryle, aralkyle, alcoxy, mercaptoalkyle, aryloxy, thiaryloxy, alcaryloxy, mercaptoalcaryle, nitro, amino, N-alkylamino, N-arylamino, N-alcarylamino, fluoro, chloro, bromo, iodo et trifluorométhyle,

R_5 est choisi parmi les mêmes groupes que R_4,

R_6 est un atome d'hydrogène, un groupe halo, trifluorométhyle ou alkyle ayant 1 à 4 atomes de carbone, à condition que lorsque R_6 est en position 7 ou 9, il ne soit pas un groupe halo,

R_8 est un atome d'hydrogène ou un groupe hydroxyméthyle,

R_9 est un atome d'hydrogène ou un groupe alkyle ayant 1 à 6 atomes de carbone, ou lorsque R_2 est un groupe hydroxy, R_9 peut être une partie de formule II dans laquelle R_9 est un atome d'hydrogène et R_2 est une liaison de réunion; ou

R_2 et R_9 peuvent former conjointement une semicarbazone,

X est un atome d'oxygène ou un groupe NR_5,

Y est un atome d'azote ou de phosphore,

et de dérivés méthylènedioxy de celui-ci à la condition que lorsque X est un atome d'oxygène, R_3 ne soit pas un groupe méthyle lorsque R_1 est un groupe méthoxy, R_2 soit un groupe hydroxy, et tous les R_4 soient un atome d'hydrogène, ou d'un sel d'addition d'acide de ceux-ci acceptable du point de vue pharmaceutique, dans la fabrication d'une préparation pharmaceutique pour le traitement de la schizophrénie.

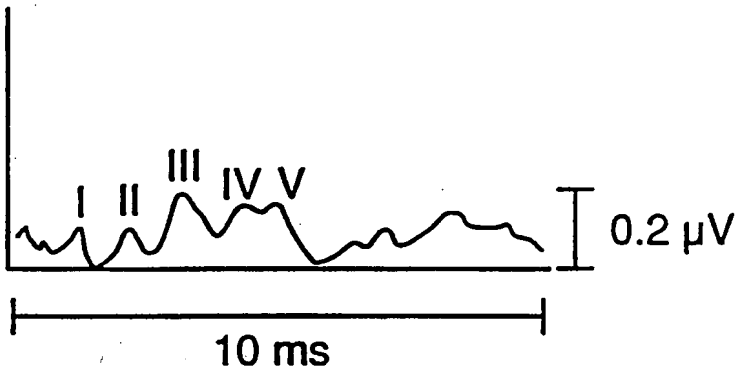


Fig. 1A

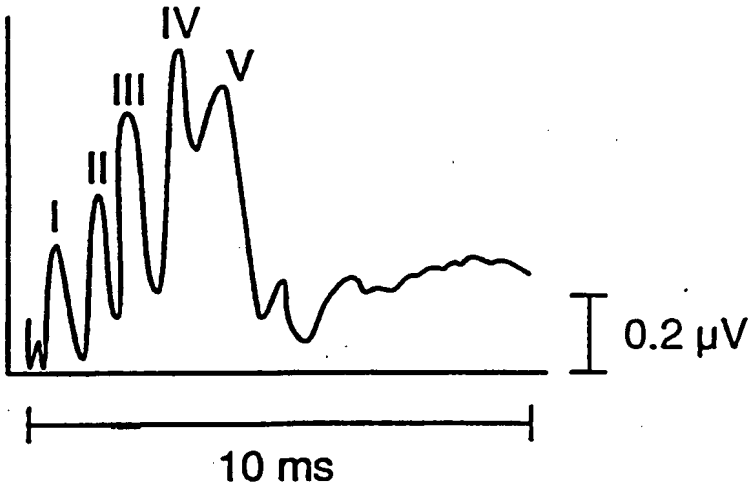


Fig. 1B

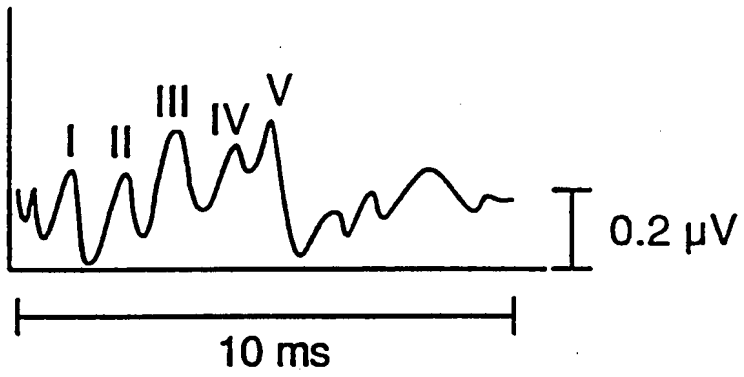


Fig. 2A

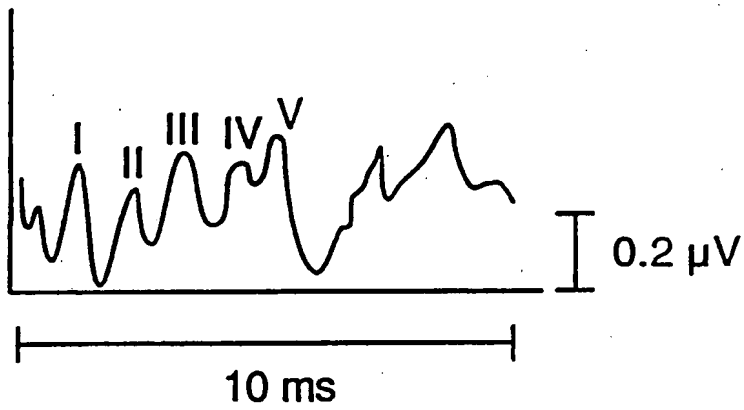


Fig. 2B